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New Findings in the Behavioral Profile of Young FraX Females

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Nine girls, with a 50% risk to be carrier of the FMR-1 gene and who attended normal school and did not have a mentally retarded fraX relative, were selected to exclude influences of external factors. These subjects were submitted to an extensive neurocognitive and psychiatric evaluation before molecular analysis of their FMR-1 status was done to obtain completely unbiased results. The findings of this study suggest that differentiation according to the FMR-1 status may be more significant at the neurocognitive level than at the behavioral level and support the hypothesis that behavioral problems are more influenced by external factors than by the FMR-1 carrier state.

KEY WORDS: young fraX females, neurocognitive functioning, behavior

INTRODUCTION

The inheritance of the fragile X syndrome is unique. Most males who carry the fragile X mutation are affected and show the clinical phenotype. Males who carry the fragile X premutation are clinically and cytogenetically normal. Mental retardation is rare among the daughters of these normal transmitting males, but learning disabilities and mental impairment are commonly found in females with the full mutation, who inherited their gene from their mothers [Staley et al., 1993].

Several studies have described the specific cognitive deficits and behavior characteristics of females with the fragile X syndrome (fraX) [Reiss et al., 1988; Borghgraef et al., 1990; Brainard et al., 1991; Sobesky, 1991; Hagerman et al., 1992; Lachiewicz 1992; Freund et al., 1993]. However, most of the results are not significant and conclusions are not always consistent. Reiss et al. [1988] described an increased rate of schizophrenia and affective disorders in his group of fraX females. Hagerman et al. [1992] observed greater shyness, poor eye contact, and sigificant attention difficulties in fraX-positive girls. The group of females with fragile X mutation reported by Freund et al. [1993] did not show higher frequency of attention deficit hyperactivity disorder (ADHD) or undifferentiated attentional deficits. At the present time, it is unclear whether the higher incidence of learning problems and behavior characteristics is an intrinsic problem of the female fraX carrier status or rather the consequence of external factors encountered by the female carriers. A study by Reiss et al. [1989] demonstrated that fraX-positive women manifested, in addition to significantly greater impairment of social, educational, and psychological functioning, a higher frequency of intermittent depressive disorder. In addition, these investigators suggested that the stress of parenting and educating a developmentally disabled fraX child may have an effect on the psychological well-being of the parent. Several methods can be applied to resolve this question.

The aim of the present study was to assess neuropsychological and psychiatric data in young fraX females who have not been exposed to the adversities of fraX carrier status, that is, rearing a fraX son or growing up with a fraX brother.

MATERIALS AND METHODS

We examined a group of 9 girls, 7–15 years old, who belonged to 7 different fraX families. Two of the subjects are sisters and 2 are nieces. All had a 50% risk to be a carrier of the FMR-1 gene mutation because FMR-1 studies in their mentally normal mothers were positive.

We tested all 9 girls extensively before molecular studies were performed (Southern blot assay with probe St.12.3 after double digestion with EcoRI and EagI) to obtain unbiased results.

Three types of testing were performed in all individuals. Intelligence was tested with the Wechsler Intelligence Scale for Children—Revised (WISC-R) [Van Haasen et al., 1986]. The second part consisted of a set of neuropsychological tests that covered a wide range of cognitive functions. The Bourdon–Wiersma test consists of a widely used cancellation task that evaluates

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TABLE I. Molecular and Clinical Data in 9 Girls at Risk to be Carriers of the FMR-1 Gene Mutation

Subjects[a]	FraX A status	CGG repeat expansion	Age
1	Normal	—	7 years 1 months
2	Normal	—	7 years 8 months
3	Normal	—	12 years 4 months
4	Mosaic	0.4 kb + smear, methylated	10 years 10 months
5	Full mutation	1.2 kb, methylated	7 years
6	Full mutation	1.6 kb + smear, methylated	9 years 9 months
7	Full mutation	1.8 kb, methylated	11 years
8	Full mutation	1.2 kb + smear, methylated	13 years 5 months
9	Full mutation	1.4 kb + smear, methylated	15 years 3 months

[a] Subjects 3 and 5 are sisters, and subjects 2 and 6 are cousins.

continuous and focused attention [Grewel, 1953; Kamphuis, 1962]; the Rey Complex Figure test measures the ability to structure and reproduce visual information [Osterieth, 1944]; the Stroop Color Word test evaluates the ability to suppress interfering stimuli [Jensen and Rowler, 1966]; and the Bender Visual Gestalt test is a drawing test [Hain, 1964].

Finally, an extended child psychiatric evaluation was performed with the Diagnostic Interview of Children and Adolescents (DICA) [Herjanic and Campbell, 1977], a structured psychiatric interview based on DSM III-R criteria. The general behavior and especially the hyperactivity was investigated by Achenbach's [1991] Child Behavior Checklist and the Conners Parents Questionnaire [Goyette et al., 1978].

RESULTS

Molecular Diagnosis

Subsequent molecular analysis was normal in 3 girls. A full mutation in the FMR-1 gene was found (all fully methylated) in 5 girls, and a premutation/full mutation mosaicism was found in 1 (see Table I).

Intelligence (Table II)

The mean IQs of the 5 girls with fraX full mutation and the 1 with premutation/full mutation mosaicism were 94 for Verbal IQ (VIQ), 82 for Performance IQ (PIQ), and 87 for the mean Full Scale IQ (FSIQ). The mean IQs of the 3 fraX-negative girls were 107 for VIQ, 114 for PIQ, and 112 for FSIQ. The IQ profile showed a different pattern in both groups: all fraX-positive girls had a higher VIQ than PIQ. In 3, the mean difference was significant. In 2 of the 3 fraX-negative girls, PIQ was higher than VIQ and at a significant level for 1 girl.

Neuropsychological Results (Tables III, IV)

The Rey Complex Figure test measures the ability to structure and reproduce visual information. In this test, the structuration-type score applies to the strategy the subject follows to copy the figure; the details score is an evaluation of the number and position of particular details in the subject's drawing. Both scores are expressed in percentiles. Bad performances on these tests are frequently observed in children with attention deficits and poor cognitive strategies. Three of 5 fraX-positive girls and 1 of the 2 fraX-negative girls had problems performing the Rey Complex Figure test. The group of fraX-positive girls performed most poorly on details when copying and memorizing the figure.

The Bourdon–Wiersma test (Dutch and French versions) consists of a cancellation task that evaluates continuous and focused attention and is used widely in the neuropsychiatric evaluation of psychiatric patients and hyperkinetic children [Grewel, 1953]. In both groups, subjects went through the test with greater variation than allowed for speed: 4 of the 6 fraX-positive girls had more "omissions" than the cutoff score, which indicates poor attention skills.

Results on the other neuropsychological tests (Stroop Color Word test and Bender Visual Gestalt test) were very heterogeneous and scanty (because of the minimal age limit of 8 years) and did not allow for any differentiation according to FMR-1 status.

TABLE II. Individual and Mean IQs in 3 FraX-Negative Girls and 6-FraX-Positive Girls

Subject	FraX A status	Age	FSIQ	VIQ	PIQ	VIQ–PIQ
1	Normal	7 years 1 month	106	107	103	4
2	Normal	7 years 8 months	93	85	105	−20[a]
3	Normal	12 years 4 months	138	130	134	−4
4	Mosaic	10 years 10 months	78	85	78	7
5	FM[b]	7 years	117	122	105	17[a]
6	FM	9 years 9 months	98	107	90	17[a]
7	FM	11 years	75	79	76	3
8	FM	13 years 5 months	74	80	70	10
9	FM	15 years 3 months	80	93	73	20[a]

[a] Mean difference between VIQ and PIQ is significant at $P < 0.05$.
[b] FM = full mutation and fully methylated.

TABLE III. Results on the Rey Complex Figure Test

		Copy		Memory	
Subject	FraX status	Structuration	Details	Structuration	Details
1	Normal	—	—	—	—
2	Normal	pc[a] 10	pc 10	pc 10	pc 0
3	Normal	pc 75	pc 75	pc 50	pc 90
4	Mosaic	—	—	—	—
5	FM[b]	pc 50	pc 50	pc 50	pc 10
6	FM	pc 50	pc 0	pc 75	pc 10
7	FM	pc 25	pc 10	pc 25	pc 10
8	FM	pc 5	pc 10	pc 50	pc 10
9	FM	pc 25	pc 0	pc 25	pc 0

[a] pc = percentile.
[b] FM = full mutation and fully methylated.

Child Psychiatric Evaluation (Table V)

Results on the DICA indicated a diagnosis of ADHD syndrome in 1 girl in the fraX-positive group and of an "adjustment disorder" with depressive mood in 1 girl in the fraX-negative group.

On the Conners Parents Questionnaire, none of the subjects reached the cutoff value for hyperactivity. The girl with ADHD had the highest score.

On the Child Behavior Checklist, the results were all within normal clinical range, except for the 2 sisters (subjects 3 and 5, 1 fraX positive and 1 fraX negative). Serious problems in child–parent interaction were noted in this family.

DISCUSSION

In a previous study, we reported specific cognitive deficits and mild pathological personality traits in a group of 11 normally intelligent, adult fraX female carriers (7 premutated and 4 fully mutated females) [Steyaert et al., 1992, 1994].

The aim of the present study was to assess neuropsychological data in young fraX females: we examined 9 girls, 7–15 years old, with the same types of testing as those performed in the adult group.

To exclude possible negative influences of external factors on behavior, we selected 9 girls who attended normal schools and did not have mentally retarded fraX relatives. In addition, the testing of the 9 subjects was unbiased because molecular examination of their FMR-1 status (normal results in 3 girls, full FMR-1 mutation in 5 girls, and premutation/fully mutated mosaicism in 1 girl) was performed only after psychological evaluation and parent interviews.

The results of the WISC-R confirmed the low normal intellectual functioning in the 6 fraX carriers (mean IQ = 87; individual IQs = 74–117), as has been demonstrated in previous studies [Kemper et al., 1986; Miezejeski et al., 1986; Borghgraef et al., 1990; Brainard et al., 1991].

The observation that 3 of the fraX-positive girls with an IQ below 80 were attending normal schools at the time of this study was surprising. Only after the diagnosis of their subnormal intellectual functioning as part of the fraX carrier state it became evident that these 3 fraX girls had difficulties in school. Possible negative school experiences, failure, and lack of social integration may be the source of low self-esteem, shyness, and anxiety in adult fraX carriers [Sobesky, 1991; Hagerman et al., 1992].

Results on the neuropsychological tests confirmed previous results in adult fraX females [Steyaert et al., 1992, 1994] and showed a deficiency on tests that require attention skills and visual memory and analysis. On the Rey Complex Figure test and on the Bourdon–Wiersma test, fraX-positive girls performed more poorly than did the control girls. The low results on the Bourdon–Wiersma attention test in the high-functioning patient 3 were unexpected and may be explained at least in part by the negative influence of emotional problems on test results.

The results on the Child Psychiatric evaluation did not confirm the findings in previous studies, reporting instead a much higher incidence of behavior problems in the group of fraX carriers [Lachiewicz et al., 1992; Lachiewicz and Dawson, 1994]; on the Conners Parents Questionnaire and the Child Behavior Checklist, the findings in the present 6 fraX-positive girls were all

TABLE IV. Results on the Bourdon Wiersma Test

Subject	FraX status	SD of speed[a]	Omissions[a]
1	Normal	+	+
2	Normal	−1	+
3	Normal	−1	+
4	Mosaic	−1	−1
5	FM	+	−1
6	FM	+	+
7	FM	−1	−1
8	FM	−1	−1
9	FM	−1	+1

[a] + = at cutoff score, −1 = below cutoff score, +1 = above cutoff score.

TABLE V. DICA Results on the Parents

Subject	FraX status	Diagnosis
1	Normal	—
2	Normal	—
3	Normal	Adjustment disorder with depressive mood
4	Mosaic	ADHD
5	FM	—
6	FM	—
7	FM	—
8	FM	—
9	FM	—

within normal limits, except for 1 girl, whose fraX-negative sister also demonstrated behavior problems. The DICA structured interview showed a psychiatric diagnosis in 2 girls, 1 fraX-positive girl presented ADHD, and 1 of the 3 fraX-negative girls had an adjustment disorder with depressive mood. These findings suggest that behavior problems in fraX carriers may be influenced more by external factors, i.e., family factors as delineated earlier, than by their FMR-1 carrier state.

Taking into account the small number of subjects and the use of available tests and questionnaires, differentiation according to FMR-1 status may be more significant at the neurocognitive level than at the behavioral level. The finding in the present study suggests that extensive child psychiatric evaluation is not adequate to detect girls at risk for fraX. Early identification and intervention in the female fraX population based on molecular studies may help decrease the risk of serious social, educational, and psychological dysfunction during their adult years.

Studies of behavior in a larger series would be necessary before neuropsychological screening can be evaluated properly.

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